Improved efficacy of antiretroviral treatment and characterization of current treatment failures in a Norwegian HIV-infected cohort

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Abstract

This is a study of the HIV cohort at the The Ullevål Department of Infectious Disease, Oslo University Hospital (IDU). We have studied the success of ART (anti retroviral therapy) on the HIV population in a historic perspective, examining success and failure rates from 1998 to 2010. Furthermore we have looked at different demographic groups in the HIV population, trying to identify whether viral transmission group, age, ethnicity or gender is predictive of ART failure.

I also studied various biological markers, both prior to treatment and current values. The aim was to identify whether biological markers exist that can predict later HIV failure, and to characterize treatment failure biologically. Looking at this information for different demographic groups, I found that different predictors exist for different transmission groups.

This publishment is a draft of an article, planned published in the near future in a journal of infectious diseases. The article will be written with Professor Dag Kvale and dr Vidar Ormåsen as co-writers. All use of results, figures and text is prohibited untill June 2015, based on an agreement between the author and University of Oslo (see “Klausuleringsregler”).

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1 Introduction

The Ullevål Department of Infectious Disease, Oslo University Hospital (IDU) has been treated HIV patients since the 1980s, and is the number one center in Norway on HIV treatment. In the beginning, anti retroviral therapy (ART) was a tough treatment, with many and grave side effects and low success rates. The introduction of HAART in the late 1990s changed these success rates radically, and its continous development in the past decade has transformed HIV from being a lethal disease to be a chronic disease for the majority of the infected, also with more moderate side effects of the treatment.

2 Methods

2.1 Selection criteria and characterization of patients

The Ullevål Department of Infectious Disease, Oslo University Hospital (IDU) holds the largest HIV cohort in Norway with 768 patients on antiretroviral treatment (ART) by 31. December 2009. An approved clinical data base for quality evaluations contains data on all of the patients followed by the clinic in the HIV era.

The criteria for inclusion were HIV seropositivity and clinical follow-up data for at least 2 years. Patients were evaluated for virological ART failure defined by HIV RNA > 400 copies/mL on at the last visit prior to analysis, provided that the patients on ART for at least 6 months.

Various patients groups were examined in relation to ART failure including age, gender, nationality of birth, and risk groups. Nationality was defined as western (European, North America, and Oceania) or non–western (South America, Asia and Africa). The larger risk groups in relation to viral transmission were defined as heterosexual (hetero), men who have sex with men (msm), are men who were infected during homosexual activity, and injecting drug users.

2.2 Statistical methods

We used the statistical program Statistica, version 7.0 for all analyses (StatSoft, OK, USA). Non-parametric tests including the Mann–Whitney U-test were generally used to characterize the study population, whereas distribution differences were calculated by Chi square.

3 Results

3.1 The decline in virological ART failure 1998-2010

The prevalence of virological ART failure on 1 January 1998 became gradually reduced from 61% to 9 % in 2010 (Fig. 1).

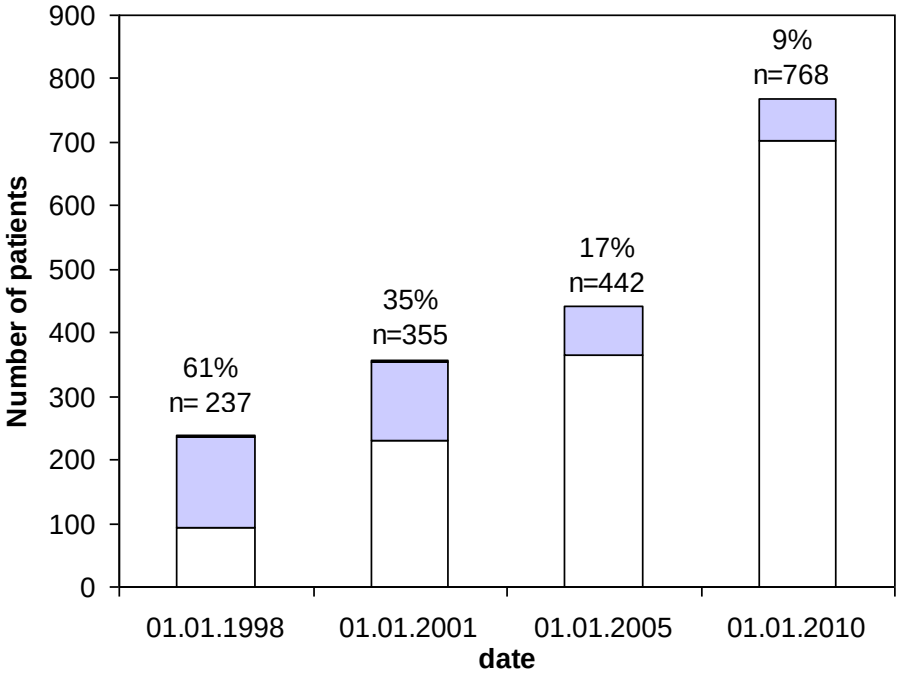

Figure 1. Patients on ART between 1998 and 2010. Percentages and shaded areas represent patients with virological failure (HIV RNA > 400 copies/mL) after at least 6 months of ART.

3.2 Predictors of treatment failure

We started our study with looking at characteristics for the patients failing, to see if they differ in age, gender, risk group and nationality compared to the HIV population as a whole, but could not demonstrate any clear characteristics of the patients failing treatment (Fig. 2). Transmission risk groups seem be to similar to international figures. In our total population, heterosexual represent 45 percent, MSM 44% and injecting drug users 8 %, an international study shows 36, 40 and 16 respectively [1].

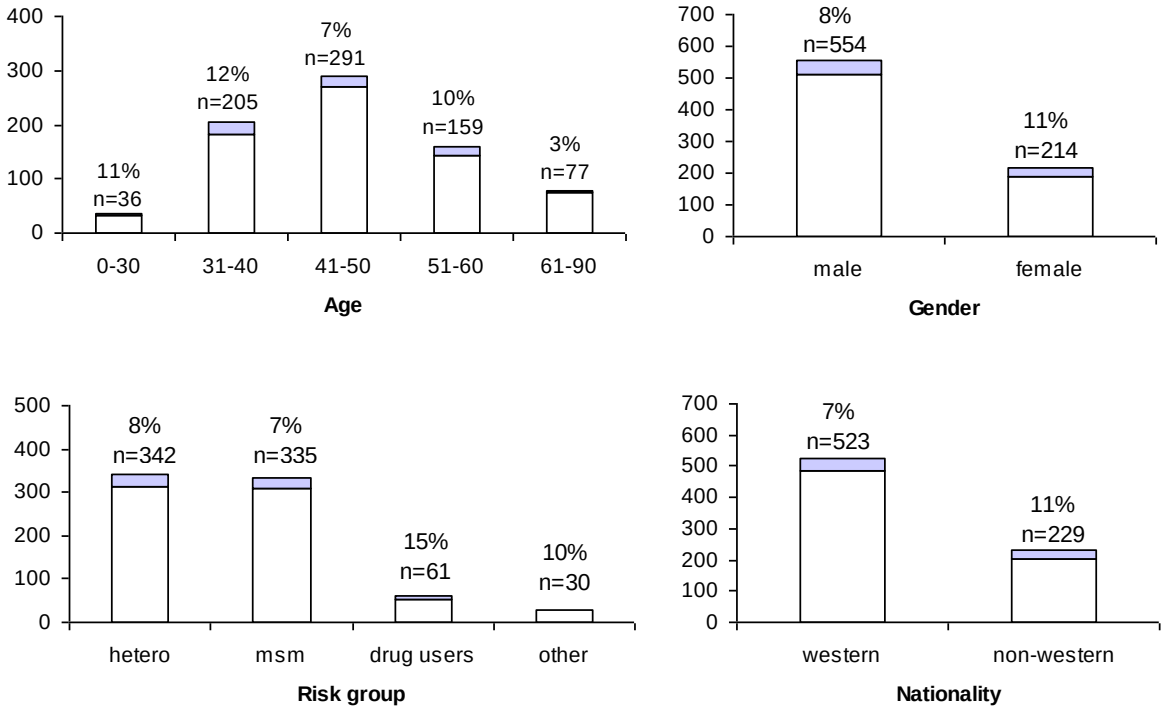

Figure 2. Demography and transmission categories of current HIV patients (1 January 2010). Percentages and shaded areas represent patients with virological failure (HIV RNA > 400 copies/mL) after at least 6 months of ART.

We also looked more in detail within these and other groups where one might could anticipate differences in ART efficacy, such as former AIDS diagnosis. To our surprise, we did not find any differences in the distribution of treatment failure patients, except a surprisingly better treatment result in patients > 60 years (p=0.04) and probably a higher rate of virological failure in injecting drug users (p=0.07) (Table 1). We also looked into females in general as well as in non-western females. Although both these groups had numerically higher failure rates, these were not statistically different (Table 1).

Table 1. Frequency of demographic groups with virological success and failure.

Patient group	Virological success (%) n=702	Virological failure (%) n=66	P*
Former AIDS diagnosis	24	20	0.56
Age > 60 years	11	3	0.04
Non-western	30	39	0.12
MSM	46	39	0.53
Injecting drug users	7	14	0.07
Females	27	36	0.11
Non-western females	15	23	0.14

p* chi square, absolute numbers.

We then examined some of available classical pre-ART parameters representing the immune constition such as CD4+ T cell counts, the virological control (HIV RNA, CD8+ count (Pettersen et al., 2010) as well as weak parameters for immune activation (β_2-microglobulin), but none of these variables were predictive for later virological ART failure for the cohort as a whole (Table 2). For some groups however, β_2-microglobulin pre-treatment proved to be a possible predictor for later failure (Figure 3). Our interpretation of this is that HAART treatment has a positive effect on the immune defense system, without restoring the immune system fully in those seriously affected by HIV infection.

Table 2. Characteristics of current study population by December 2009.

Median values with IQ range.

	Current HIV RNA		
	< 400 (n=702)	> 400 (n=66)	P*
Pre treatment values			
CD4	190 (110-270)	180 (120-250)	0.76
CD8	975 (630-1415)	860 (565-1280)	0.22
CD4/CD8 ratio	0.17 (0.11-0.29)	0.19 (0.13-0.29)	0.30
HIV RNA	130' (40' – 410')	110' (44'-430')	0.64
β_2-microglobulin	2.9 (2.2-3.6)	3.0 (2.4-3.7)	0.70
Age	37 (31-44)	34 (29-40)	<0,01
Current values (on treatment)			
CD4	522 (370-671)	355 (198-559)	<0.01
CD8	1009 (753-1368)	1183 (830-1695)	0.03
CD4/CD8 ratio	0.51 (0.34-0.75)	0.30 (0.20-0.39)	<0.01
HIV RNA	2 (0-2)	4800 (1000-51000)	<0.01
β_2-microglobulin	1.9 (1.6-2.3)	2.7 (2.2-3-4)	<0.01
Hb	14.3 (13.2-15.2)	13.6 (12.1-14.6)	<0.01
Albumin	44 (42-46)	43 (40-45)	<0.01
Age	46 (39-53)	44 (37-51)	0.07
Months of treatment	76 (35-139)	79 (37-139)	0.73
Months of HIV diagnosis	114 (66-188)	125 (84-198)	0.11

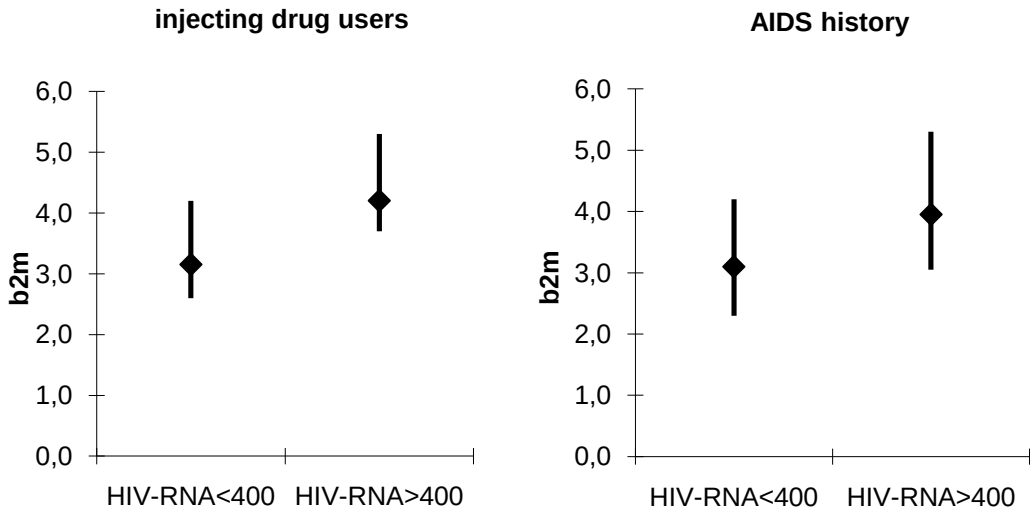

Figure 3. Pre-treatment beta-2 microglobulin values for two demographic groups of HIV-patients on HAART, intra-venous drug users and patients with former AIDS history. Cathegorisation by current HIV-RNA values, values above 400 copies/mL defined as virological failure. Diamonds mark median values, lines mark the 25-75% interval.

We also examined the patients' age at the time of treatment start, and to our surprise low age proved to be a significant predictive factor for later treatment failure, an opposite finding to what we would have postulated (Table 2). Further examination of the data showed that young age as a predictive factor for later treatment failure is mainly an issue for MSM, where median age pre treatment is 7 years younger among those failing treatment compared to those were treatment is successful. No such difference in age is to be seen in the other large demographic group, heterosexual women. MSM failing treatment also have a significantly higher CD4/CD8 ratio, which is also contradictory to what we would have postulated (Table 3).

Table 3. Characteristics of current study population, heterosexual females cohort and MSM cohort, December 2009. Median values with IQ range.

	Heterosexual females - current HIV RNA			MSM - current HIV RNA		
	< 400 (n=155)	> 400 (n=21)	P*	< 400 (n=310)	> 400 (n=25)	P*
Pre treatment values						
CD4	190 (100-250)	146.5 (50-250)	0.29	180 (104-260)	190 (130-260)	0.52
CD8	736 (520-1232)	735 (515-1020)	0.54	1060 (701-1460)	1090 (510-1390)	0.64
CD4/CD8 ratio	0.19 (0.11-0.37)	0.20 (0.09-0.20)	0.41	0.17 (0.098-0.26)	0.22 (0.14-0.36)	0.046
HIV RNA	79' (21'-220')	235' (39'-600')	0.045	155' (48' – 490')	205' (87'-530')	0.42
β_2-microglobulin	2.4 (1.7-3.1)	2.85 (1.80-3.70)	0.31	3.0 (2.3-3.8)	2.9 (2.4-3.1)	0.52
Age	30 (27-37)	32.5 (29-37)	0.39	40 (34-46)	33 (28-37)	<0.01
Current values (on treatment)						
CD4	517 (370-671)	323 (188-402)	<0.01	545 (405 – 699)	525 (351 – 706)	0.45
CD8	900 (653-1208)	1019 (746-1291)	0.33	1069 (821 – 1474)	1365 (971-2220)	0.03
CD4/CD8 ratio	0.56 (0.41 – 0.84)	0.30 (0.21-0.37)	<0.01	0.51 (0.34-0.73)	0.33 (0.219-0.55)	<0.01
HIV RNA	0 (0-2)	6700 (1400-51000)	<0.01	2 (0-2)	2000 (980-20000)	<0.01
β_2-microglobulin	1.6 (1.3-2.0)	2.65 (2.250-3.65)	<0.01	2.0 (1.7-2.3)	2.55 (2.0-3.15)	<0.01
Hb	12.7 (12-13.4)	11.6 (11.0-12.7)	<0.01	14.9 (14.3-15.5)	14.6 (14.1-15.35)	0.47
Albumin	43 (41-44)	40.5 (35-43)	<0.01	45 (43-46)	45 (41-48)	0.82
Age	39 (34-45)	40 (35-49)	0.37	48 (41-56)	42 (38-50)	<0.01
Months of treatment	70 (38-121)	77 (48-118)	0.61	76 (28-144)	85 (62-145)	0.22
Months of HIV diagnosis	92 (63-149)	120 (89-153)	0.049	123 (66-201)	150 (90-183)	0.26

* Mann Whitney analysis

We then looked at the current data of the population. Looking at all patients failing treatment as a whole, keeping with a concurrent median viraemia at 4800 HIV RNA copies/mL, these patients are clearly affected by their treatment failure by having substantially lower CD4 counts and higher immune activation in terms of β_2-microglobulin. Levels of hemoglobin and albumin are also significantly lower. Their duration of treatment and length of HIV infection is similar to patients treated with success (Table 1). Heterosexual women failing treatment have a significantly longer time of HIV diagnosis that women treated with success, while time of treatment is similar (table 3).

MSM failing treatment seem to be less affected by their treatment failure, they have similar CD4 but significantly higher CD8 counts than MSM who experience successful treatment. They keep being significantly younger in age at time of failure than those treated successfully (table 3).

4 Discussion

Our study has shown that the introduction of HAART in the late 1990s has had a great impact on the success rates in the treatment of HIV. Prevalence of virological failure has continously decreased from 61 percent in 1998 to 9 percent in 2010, leaving little doubt that HIV treatment is continously improving. An international study from 2006 shows similar findings [1].

Stratifications show little difference of treatment failure between different demographic groups. This may be partly due to small groups. Patients of high age have a significant lower failure rate than the younger patients. A european observational study has found similar data, that probability of virological response is higher for the older patients [2]. This may be due to longer period of treatment or better compliance. There is also a trend that injecting drug users fail more often, compliance is most likely an important factor also here. An earlier study shows that injecting drug users experience substantially increased rates of AIDS and death up to 6 years after starting HAART [3].

Earlier studies show that identifying biological markers for later HIV treatment failure is difficult [4]. In our study, there is trends that a high level of beta-2 microglobulin before treatment may be used as a marker of later treatment failure for some patient groups. This marker, which is increased in serum during immune activation, has been widely recognised as a marker for HIV infection and progressive disease since the 1980s [5,6,7]. A study from Edinburgh indicate that for drug users changes in beta2 microglobulin levels may reflect differences in drug-injecting behavior and are not influenced by HIV status or progression alone [8].

Young age seems to be an important predictor of later treatment failure, especially for MSM. We have no clear explanation for this, but compliance is possibly a factor to be considered. For women, a high HIV-RNA count prior to treatment and a long time of HIV diagnosis is predictive of failure, which is not surprising.

Virological failure seems to be associated with an unfortunate activation of the immune system, with high CD8, low CD4/CD8 ratio and high beta-2 microglobulin values. This activation occurs despite low viral counts.

Time of treatment seems to be of little importance for virological failure for our HIV population as a whole. Earlier studies describe treatment exhaustion in HAART as a “danger to a substantial proportion of patients” [9]. We have found length of HIV diagnosis to be a significant prognostic factor for treatment failure, but time of treatment is not prognostic, indicating that for our population, time prior to treatment is more relevant than long treatment with treatment exhaustion.

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